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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,131	09/13/2005	Caroline Rougaignon	GEI-103	2459

47888 7590 01/25/2008

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EXAMINER	
HOUGHTLING, RICHARD A	

ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
01/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,131	ROUGAIGNON ET AL.	
	Examiner	Art Unit	
	Richard A. Houghtling, Ph.D.	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 February 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-22 are pending in this application and are examined on their merits, herein.

Priority

2. Applicants' claim to foreign priority to FR 0210068 is acknowledged and entered in the record.

Drawings

3. The drawings are objected to because the titles and axes are composed in French and are not translated to English. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are

not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

4. Claim 13 is objected to because of the following informalities: 1) a typographical error is found wherein a reference is made to the pharmaceutical composition of claim 11 which should instead read claim 12; and 2) when a trademark is used in a claim, it must be in all capitalized letters. Appropriate correction is required.

5. Claims 2-20 are objected to because of the following informalities: proper dependent claim form requires reference to "The" pharmaceutical composition as opposed to "A" pharmaceutical composition as written. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 13 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 is drawn to a pharmaceutical composition which further limits the suspension agent of claim 11 to that of the semisynthetic glycerides WITEPSOL® or SUPPOCIRE®. It is unclear from the specification as to what is encompassed by these two trademarks.

Claim 20 is drawn to a pharmaceutical composition, allowing T maxs of oxybutynin to be obtained between approximately two hours and approximately sixteen hours wherein the excipient or the vehicle is selected so that the speed of release is as long as possible.

The claim terminology "speed of release is as long as possible" is indefinite, because it is unclear what is meant by the term "speed" and what property of drug release is to be affected.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-9, 14-15 and 19-22 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Guittard et al. (U.S. Patent 6,262,115).

The claimed invention is drawn to a pharmaceutical composition comprising oxybutynin, in combination or not with a moderated estrogen and a pharmaceutically acceptable excipient intended for vaginal or rectal administration (claim 1) or a method for treating urinary incontinence comprising administering the pharmaceutical composition of claim 1 (claim 22). Dependent claims 2-4, each further limit the pharmaceutical composition of claim 1 by Markush groups that define oxybutynin to the base, its addition salts with a mineral or organic acid and their epimers (claim 2); the moderated estrogen is estriol, estradiol and esters and mixed ethers of estriol and estradiol (claim 3); and the form is a suppository, vaginal capsule, rectal capsule and a gel (claim 4).

Dosing of the pharmaceutical composition of claim 1 is further limited to: 1-25 mg of oxybutynin or its salts (claim 5), which is further limited to 5-15 mg of oxybutynin hydrochloride (claim 6), the moderated estrogen is to be dosed at 0.01mg-5 mg (claim 7); which is further limited to estriol at a dose of 0.1 mg-2 mg (claim 8) or is further limited to estriol at a range of 0.2 mg-1 mg (claim 9). The pharmaceutical composition of claim 1 further contains one or more gelling agents, (claim 14) which is/are cellulose derivatives (claim 15).

Claims 19-21 each depend from the pharmaceutical composition of claim 1, and further define properties of the drug release. Sustained release of active ingredients, spread over more than twenty-four hours, wherein the fatty material in which the oxybutynin hydrochloride is placed in suspension (claim 19); or a composition which the excipient or vehicle is selected so that the speed of release is as long as possible (claim 20); or the excipient or vehicle is selected so that the administration of oxybutynin takes place once, or optionally twice, per twenty four hours (claim 21).

Claim 22 is drawn to a method for the treatment of urinary incontinence in humans comprising administering to humans in need thereof an amount of a composition of claim 1 sufficient to treat urinary incontinency.

Guittard et al. teach pharmaceutical compositions, dosage forms comprising oxybutynin alone or in combination with other drugs, as well as, a method for management of incontinence by administering oxybutynin alone or combined with other drugs (see abstract; col. 1, lines 20-25; see Example 23, col. 19, lines 25-41). The pharmaceutical composition comprises oxybutynin (240 ng to 650 mg; see col. 3, lines 11-13; as well as see Example 21 found in col. 18, lines 60-67) or a pharmaceutically acceptable salt (i.e., hydrochloride; see col. 3, lines 14-21; and see col. 16-17, Examples 11, 13-15). Furthermore, oxybutynin may be used as its racemate, S-enantiomer or R-enantiomer (col. 3, lines 21-22). In addition to oxybutynin, additional drugs such as steroids—progestin or estrogen may also be used alone or together (col.

3, lines 32-col. 4 lines 1-23; and see col. 18-19, Examples 20-21). Many estrogen steroids which may be utilized include estriol, estradiol and esters, ethers and mixed ethers of estriol and estradiol (col. 3, lines 57-67 to col.4 line 1; and see col. 19, Example 22) and the doses of the estrogens may range 10 ng to 600 mg (col. 4, lines 2-4; and see col. 19, Example 22). Administration of oxybutynin alone or combined with other therapies includes manufacture of a single drug which results in the dissolution or release of the drug over a 24 hour period of time (col. 4, lines 41-44; and see Examples 16-19 spanning col. 17-18). The pharmaceutical composition taught may be manufactured as a hydrogel osmopolymer (col. 11, lines 27-32). One of the components of the hydrogel is hydroxypropylmethylcellulose (see col. 16, Example 14). And finally, Guittard et al. disclose both an immediate release formulation which is administered every 8 hr as well as a controlled release formulation wherein it is administered once in 24 hr. Both the immediate release and the controlled release formulation and single *versus* multiple dosing regimens of the controlled release formulation resulted in similar $plasma_{AUC}$ values (see col. 20 lines 51-67 and col. 21, lines 1-10). Therefore, each and every limitation of instant claims 1-9, 14-15 and 19-22 are met by the teachings and disclosure by Guittard et al. '115.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 10-13 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guittard et al. as applied to claims 1-9, 14-15 and 19-22 above, and further in view of *Remington's: The Science and Practice of Pharmacy*, Nineteenth Edition, Vol. I,1985, pp. 957 and 960 and Berko et al. (2002, see PTO-892).

Applicants' invention drawn to a pharmaceutical composition of claim 1 is further modified by dependent claims 10-13 and 16-18. The pharmaceutical composition may also include one or more suspension agents (claim 10), which are bioadhesive silicic acid derivatives (claim 11). The excipient is a fatty phase formed by semisynthetic glycerides (claim 12), which are WITEPSOL® or SUPPOCIRE® (claim 13). Additionally, a carbomer (claim 16) which is a polycarbophil in acid or salified form (claim 17) or a calcium salt (claim 18) may be included.

Guittard et al. do not teach the specific bioadhesive silicic acid derivatives, the semisynthetic glycerides, WITEPSOL® or SUPPOCIRE®, or teach the inclusion of a carbomer.

Remington's: The Science and Practice of Pharmacy, Nineteenth Edition, Vol I, 1985, pp. 957-960 teach that the inclusion of a bioadhesive permits close contact of agents to the mucous lining and further limits the transit so that a high concentration gradient across the membrane may be maintained for an extended period of time. Furthermore, polycarbophil and other polyacrylic acid-based polymers are known to chelate calcium ions in physiological buffers, which may be beneficial in increasing paracellular transport or serve to form matrices or improve the bioavailability of a drug (see p. 960). Furthermore it is well established that polycarbophil is especially useful for prolonging drug delivery for vaginal applications (see p. 957).

At the time of Applicants' invention, it would have been obvious to one of ordinary skill in the art seeking to re-formulate the oxybutynin therapy taught by Guittard et al. for an extended release formulation. Because the prior art teaches that management of incontinence using localized drug delivery via vaginal or rectal suppositories, it would have been obvious to one of ordinary skill in the art to employ the polycarbophil as taught by *Remington's: The Science and Practice of Pharmacy* and re-formulate the oxybutynin as taught by Guittard et al. in order to extend the release of the oxybutynin and reduce the frequency of drug administration. Furthermore, because *Remington's:*

The Science and Practice of Pharmacy teaches that carbophil chelates calcium ions, it would be obvious to one of ordinary skill in the art to use a calcium salt.

Remington's: The Science and Practice of Pharmacy Nineteenth Edition, Vol I, 1985, pp. 957-960 does not teach the semisynthetic glycerides WITEPSOL® or SUPPOCIRE®.

Berko et al. teach formulations of suppositories using WITEPSOL® or SUPPOCIRE® bases and the differences in release of a drug over time (see p. 313, Figure 1), as well as the effect of different surfactant concentrations on drug release (see p. 314, Figure 3). Berko does not teach oxybutinyn.

At the time of Applicants' invention, one of ordinary skill in the art seeking to re-formulate the oxybutynin for a prolonged controlled release in the form of a suppository for rectal or vaginal use would have found it obvious to employ the bases taught by Berko et al, because these bases are art accepted and would merely require optimization of the oxybutynin bioavailability for the treatment of incontinence, which is well within the purview of a skilled artisan to optimize results.

Conclusion

1. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard A. Houghtling whose telephone number is (571) 272-9334. The examiner may normally be reached Mon-Thurs 8:30 am - 5:00 pm and alternate Fridays 8:30 am - 12:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan may be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Richard A. Houghtling, Ph.D.

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER